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Case report

A novel case of a raised testosterone and LH in a young man

Tim J. McDonald [a,*,1], Mandy H. Perry [a,1], Angus G. Jones [b], Mollie Donohoe [b],
Maurice B. Salzmann [a], John O'Connor [a]

[a] Clinical Chemistry, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
[b] Department of Endocrinology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

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ABSTRACT

A 19 year old male attended his GP with a history of "fluid retention", lack of libido and erectile dysfunction. He was found to have a high serum testosterone, and a raised luteinising hormone. After further investigations, the patient admitted to taking a supplement called ActivaTe Xtreme™, obtained from an internet source, to address his low libido.

ActivaTe Xtreme™ contains active ingredients which increase serum testosterone levels by several independent mechanisms that are not associated with luteinising hormone suppression. Urine analyses for synthetic anabolic steroids were negative, and urinary testosterone, epitestosterone and other androgens were normal. This biochemical pattern is not the same as that seen with anabolic steroids (i.e. raised testosterone, suppressed luteinising hormone and abnormal urine steroid profile).

The issue of self medication with performance enhancing compounds needs to be carefully considered in order to avoid expensive and invasive investigations, missing an underlying pathology or misdiagnosing a patient. This case also raises the spectre of yet another "performance enhancing" product that may cause difficulty for those trying to ensure that sport remains on a "hormonally" equal basis.

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1. Case

We present the case of a 19 year old male student who attended his General Practitioner with a history of "fluid retention", lack of libido and erectile dysfunction. There was no further history available at this point. Routine blood tests along with serum thyroid stimulating hormone (TSH), prolactin and testosterone were requested (Table 1). On the basis of the raised testosterone the laboratory added luteinising hormone (LH) and follicular stimulating hormone (FSH) to investigate the suspicion of exogenous testosterone administration. Inhibition of the pituitary axis would be expected with use of testosterone supplements.

However, an abnormally high LH level was found. This raised suspicion of a possible LH-secreting pituitary lesion (LH-oma), analytical interference (such as heterophilic antibodies) or exogenous sources of LH or human chorionic gonadotrophin (hCG) analogues. Further investigations included serum hCG, alpha-fetoprotein (AFP), oestradiol and sex hormone binding globulin (SHBG) (Table 1). It is recognised that some young men, particularly those who are involved in body building, are aware of the use of exogenous hCG in conditions of lowered libido or to maintain testicular volume while using exogenous testosterone [1]. In this case, the normal hCG level confirmed that the raised LH was not caused by cross reactivity of exogenous hCG (Roche report cross reactivity of <0.1% with hCG, FSH, Thyroid stimulating Hormone and Growth Hormone) and the raised oestradiol was assumed to be originating from the aromatisation of the high levels of testosterone. This substantiated suspicion of an LH-oma.

Before the patient was referred to the endocrine team, we asked the GP to consult the patient regarding possible causes of the unusual gonadotrophin profile and to enquire about self medication. The patient subsequently admitted to taking ActivaTe Xtreme™ obtained from an internet source. He explained that he had "researched" this product on the internet as he had low libido and wanted to address this problem. The patient reported that he had stopped taking the compound several weeks prior to the phlebotomy, although this statement could not be confirmed or refuted.

It was felt that the patient's raised testosterone was likely to have been generated by an exogenous source and urine samples that had been collected at the same time were sent to a sports medicine toxicology laboratory for further testing (Professor David Cowan, Drug Control Centre, King's College London). Urine analyses for synthetic anabolic steroids were negative, and tests for urinary androgens were normal. The urine testosterone was not elevated and neither was the testosterone to epitestosterone ratio (0.2). Similarly, the urine testosterone to LH ratio was not elevated (<1 nmol/IU), but the urine LH concentration (70 IU/L) was considered high.

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* Correspondence author at: Peninsula College of Medicine and Dentistry, Barrack Road, Exeter, Devon, EX2 5DW, UK. Tel.: +44 1392 406758; fax: +44 1392 406767.
E-mail address: Tim.McDonald@rdeft.nhs.uk (T.J. McDonald).

[1] These authors contributed equally to the paper.

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Table 1
Routine blood test results along with TSH, prolactin and testosterone requested at presentation. Serum hCG, AFP, oestradiol and SHBG. All assays performed on the ROCHE Modular E170 and P unit platform (Roche Diagnostics, Mannheim, Germany).

Analyte	Result	Reference range	Units
Albumin	51.0	35–50	g/L
Calcium	2.2	2.05–2.55	mmol/L
TSH	2.1	0.35–4.5	miu/L
Prolactin	282.0	86–324	mu/L
Testosterone	41.0	9–27.8	nmol/L
FSH	3.2	1.5–12.4	IU/L
LH	17.7	1.7–8.6	IU/L
hCG	<1	0–4	IU/L
AFP	<1	0–6	kiu/L
Oestradiol	200.0	28–158	pmol/L
SHBG	28.0	10–80	nmol/L

2. Patient follow-up

We remained concerned that there may be an underlying endocrine pathology that prompted this patient to obtain ActivaTe Xtreme™ in the first instance. However, the results of blood tests undertaken 1 month later (Table 2) were all within normal limits and we concluded that ActivaTe Xtreme™ was indeed the likely explanation for the abnormal blood biochemistry.

Although this case could be considered a “biochemical novelty”, the issue of self medication with performance enhancing compounds needs to be carefully considered in order to avoid expensive and invasive investigations, missing an underlying pathology or misdiagnosing a patient.

3. Discussion

3.1. What is ActivaTe Xtreme™?

ActivaTe Xtreme™ is marketed as a dietary supplement for testosterone optimisation and is mainly targeted at body builders and athletes. It is unregulated, freely available to buy and legal. The manufactures suggest it may enhance sexual function, but this is not the main role for this “designer” compound.

ActivaTe Xtreme™ works by 3 different mechanisms to increase serum testosterone concentration, without causing negative feedback at the pituitary. Stinging nettle (*Urtica dioica*) root, Horny Goat Weed (*Epimedium sagittatum*) and Ceylon spinach (*Basella alba)* extracts all influence testosterone homeostasis in different ways, as discussed below.

Stinging nettle root contains the natural compound 3,4-divanillyltetrahydrofuran (Divanil$^{\mathrm{TM}}$), which binds to SHBG with a higher binding affinity than testosterone, leading to an increase in serum free testosterone. The affinity of 3,4-divanillyltetrahydrofuran to human SHBG is $3.2 \pm 1.7 \times 10^6\ \mathrm{M}^{-1}$, as determined by in vitro assay [2].

Epimedium, also called “Horny Goat Weed”, has previously been attributed as a remedy for sexual dysfunction, fatigue and libido enhancement. The effects of Epimedium are attributed to the flavanol Icariin, which has been used for many years in traditional Chinese medicine for treatment of erectile dysfunction (ED). The erectogenic effects of icariin are attributed to cGMP-specific phosphodiesterase type 5 (PDE-5) inhibitor activity [3,4]. Phosphodiesterase type 5 is a vasoconstrictor, so inhibition of this enzyme leads to vasodilation. Sildenafil, vardenafil and tadalafil, are drugs used for treatment of erectile dysfunction, also works by inhibition of this enzyme. The erectogenic effect of PDE-5 inhibitors requires a minimal nitric oxide (NO) signal triggered by sexual stimulation for effect. Treatment of ED with PDE-5 inhibitors has limited effect if cavernosal nerve injury has occurred (e.g. prostatectomy or severe diabetic neuropathy) and NO synthesis is therefore impaired. It has also been postulated that icariin may increase nitric oxide synthase (NOS) activity secondary to increased expression of NOS isoforms therefore contributing to its erectogenic effects [5].

Table 2
Blood biochemistry results measured 1 month after initial consultation.

Analyte	Result	Reference range	Units
Prolactin	141.0	86–324	mu/L
Testosterone	16.5	9–27.8	nmol/L
Oestradiol	126.0	28–158	pmol/L
SHBG	24.0	10–80	nmol/L

Of particular interest to this case report are the testosterone mimetic properties of icariin. In a study by Zhang et al., two groups of chemically-induced hypoandrogenic male rats were treated with and without icariin. The group treated with icariin demonstrated an increase in the circulating levels of testosterone and suppression of apoptosis of penile cavernosal smooth muscle compared to the control group [6]. The underlying mechanism behind the testosterone-like activity of icariin is not understood, but it is likely to mainly affect the testes, given that no difference in serum levels of LH and FSH was observed between the icariin and control groups.

ActivaTe Xtreme™ also contains extracts of Ceylon spinach, of which the active component is indole-3-carbinol (I3C). I3C is a naturally occurring phytochemical found in vegetables such as broccoli and cabbage. The manufacturers claim that this plant extract promotes testosterone production in the testes, and Ceylon spinach has been shown to stimulate Leydig cells directly in rats, leading to significant increases in testosterone output [7]. However, Brown et al. found that a cocktail of androgen precursors and herbal extracts including I3C did not cause a rise in free or total testosterone [8].

The predominant mode of action of I3C in ActivaTe Xtreme™ is the modulation of oestrone metabolism. I3C drives oestrone via the 2-hydroxylation pathway, one of the two competing hydroxylation pathways of estrone conversion, which results in the formation of metabolites with non-estrogenic properties [9]. In this case the high testosterone does not lead to a substantial increase in oestradiol as would be expected; this may be because of the modulating effects of I3C on oestrone metabolism towards the 2-hydroxylation rather than to oestradiol by 17β-dehydrogenase. Although the oestradiol is above the reference range, it is modest relative to the testosterone levels resulting in a decreased oestradiol:testosterone ratio. The free testosterone may be higher than the total testosterone suggests as a result of the SHBG displacing actions of 3,4-divanillyltetrahydrofuran. It is known that a low oestradiol:testosterone ratio leads to an increase in LH production, even when testosterone levels are in the normal range [10]. The elevated LH level would subsequently contribute to endogenous testosterone production by the testes. This biochemical pattern is seen in men treated with aromatase inhibitors that are used to lower plasma oestradiol: testosterone ratio with a corresponding rise in LH [10].

It is claimed that ActivaTe Xtreme™ does not contain any anabolic steroids in the supplement and that the testosterone increasing properties can all be attributed to the actions of stinging nettle (*Urtica dioica*) root, Horny Goat Weed (*Epimedium sagittatum*) and Ceylon spinach (*Basella alba)* extracts. However, we cannot exclude the fact that the supplement maybe contaminated with testosterone or another steroid that is metabolised to testosterone. In addition, our hypothesis that the elevated LH in this case is the result of decreased oestradiol: testosterone ratio cannot be proved and warrants further investigation.

To summarise, the manufacturers claim ActivaTe Xtreme™ increases serum testosterone levels by:

- increasing free testosterone (the result of competitive binding of SHBG by 3,4-divanillyltetrahydrofuran)
- mimicking the effects of testosterone by an unknown mechanism (by the cGMP-specific phosphodiesterase inhibitor, icariin)
- stimulating Leydig cells to increase testosterone output (modulated by indole-3-carbinol)

- increasing LH production, a result of a decrease in oestradiol: testosterone ratio secondary to decreased peripheral aromatisation of androgens (modulated by indole-3-carbinol) with subsequent increase in endogenous testosterone production.

The overall health risk of taking ActivaTe Xtreme™ supplementation is similar to those abusing any anabolic androgenic steroids. These include psychological effects (aggression, dysthymia and psychosis) and the physical effects including acne, hypogonadism, gynecomastia, tendon rupture, cardiovascular disease, abnormal liver function and increased risk of prostate cancer [11,12].

The development of ActivaTe Xtreme™ is a very clever piece of biochemical trickery. This case highlights a novel biochemical pattern that we should be aware of; a raised testosterone that is not associated with a suppressed LH and warrants further investigation. However, obtaining ethical permission to fully assess ActivaTe Xtreme™ and its effects would be difficult. ActivaTe Xtreme™ is popular amongst body builders and does not lead to the usual biochemical pattern seen with anabolic steroids (i.e. raised testosterone, suppressed LH and abnormal urine steroid profile). There is a risk therefore, that the use of this product may cause unwarranted investigations and concern regarding the underlying pathology of a patient.

This case also raises the spectre of yet another "performance enhancing" product that may cause difficulty for those trying to ensure that sport remains on a "hormonally" equal basis.

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